REMARKS

Claims 1-17 are currently pending in this application, claims 13-15, and 17 were withdrawn from consideration and claims 1-12, and 16 were rejected. Claim 1 has been amended incorporating the expression "and the membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres, and spiral wounds" into the claim. Support for the amendments to claim 1 can be found on page 16, lines 10 and 12 to 13 of the specification. Claim 16 has been cancelled and claims 18-20 have been newly added. Support for new claim 18 can be found in cancelled claim 16. Support for new claim 19 can be found in claim 15, and support for new claim 20, can be found on page 26, line 18 of the specification.

Applicants acknowledge the Interview Summary attached to the Office Action which accurately reflects the telephonic interview of September 23, 2008. Further, applicants also wish to draw to the Examiner's attention co-pending application US Appl. No. 11/579,675 which application is titled "Antisolvent Emulsion Solidification Process."

Reconsideration and allowance of the claims is respectfully requested in view of the foregoing amendments and the following remarks.

1. Claim16 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. According to the Examiner, since the method does not recite any particular step it is unclear what is meant by "using the process." Applicants have cancelled claim 16 and accordingly this rejection of claim 16 is now moot. Withdrawal of the rejection is respectfully requested.

2. Claims 1-3, 5-8, 10, and 16 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious.

Claims 1-3, 5-8, 10 and 16 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jakupovic et al. (US Patent 6,221,398, Jakupovic hereinafter) as set forth on pages 4 to 8 of the office action. According to the Examiner Jakupovic teaches a process

for producing a pharmaceutical powder for inhalation comprising crystalline particles of an inhalation compound, comprising dissolving an inhalation compound to be provided in crystalline form in a solvent, and introducing the solution containing the inhalation compound in droplet form or as a jet stream into an anti-solvent which is miscible with the solvent and which is under agitation, under non-supercritical conditions. The Examiner further asserts that Jakupovic teaches that once the compound is dissolved the solution is preferably added to the antisolvent through a porous filter having pores of 10-60 microns. According to the Examiner Jakupovic discloses in an illustrative example the use of budenoside and also discloses that the process may be used to prepare carbohydrates (saccharides). Jakupovic is however silent whether the process is continuous or not as stated by the Examiner. The Examiner asserts however that the skilled artisan would have been motivated to make the process as taught by Jakupovic a continuous process to result in a more efficient chemical manufacture.

In response applicants submit that Jakupovic discloses a batch process for producing pharmaceutical powder for inhalation which powder comprises crystalline particles of an inhalation compound. In this process an inhalation compound to be provided in the form of crystalline particles is dissolved in a solvent, after which the solution containing the inhalation compound is introduced in droplet form or as a jet stream into an antisolvent which is miscible with the solvent and which is under agitation, under non-supercritical conditions (see column 2, lines 26 to 34 of Jakupovic). The solution is introduced into the antisolvent for example through a porous filter or one or more nozzles (see column 2, lines 63 to 65). Exemplified are batch-type preparation processes wherein use is made of Pyrex Glass Filters having pores of 10 to 160 microns (column 4, lines 24 to 27).

In contrast to Jakupovic, the claimed invention (claim 1) requires that the process is a continuous process whereby use is made of a membrane which is positioned in a membrane module which membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres, or spiral wounds. The presently claimed invention provides an improved antisolvent solidification process which does not have the disadvantages of a batch crystallization process (see page 20, lines 12-16, of the specification), which can be easily scaled up to a higher volume and enables a robust control of the particle size (see page 5, lines 19-21, of the specification). This can be achieved as in the claimed invention by providing an antisolvent solidification process wherein a liquid medium comprising at least one dissolved organic or inorganic compound is introduced into one or more antisolvents, or

vice versa, and which process is operated continuously (see page 20, line 16). Continuous operation is achieved by introducing the liquid medium into the antisolvent(s) by forcing it through a membrane which is positioned in a membrane module which membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres, or spiral wounds (see page 16, lines 17-21), or vice versa. Such process as in the claimed invention can be easily scaled up to a higher volume (see page 21, lines 6-11).

Applicants submit that Jakupovic fails to teach or suggests to the skilled artisan to modify the batch process to arrive at the claimed continuous process. The Examiner's conclusory statement of alleged motivation to result in a more efficient chemical manufacture fails to meet the required burden to show prima facie obviousness. Applicants submit that the batch process as in the cited reference cannot be simply modified/redesigned to arrive at the claimed continuous process. Critical aspect is that the ratio solvent/ antisolvent should not shift during the process. This shift would result in an increase of solubility of the organic or inorganic compound. Accordingly, the particle size of the resulting crystalline particles increases over time. A robust control of the particle size is not guaranteed in a continuous process using Pyrex Glass Filter as disclosed in Jakupovic.

Furthermore, Jakupovic does not provide any indication that Pyrex Glass Filters can be easily exchanged for a membrane. More particularly, it has been found that the hydrodynamics in the process of the present invention are the same on small scale as well on large scale. The mixing process in the membrane module remains the same whether the process is carried out on laboratory scale or in the factory. Accordingly, the process of the presently claimed invention is easily scaled-up. However, the hydrodynamics in the batch process of Jakupovic will change during scale-up. Therefore, the particle size of the resulting crystalline particle will change in the process as disclosed by Jakupovic.

Thus it is clear that the process according to the presently claimed invention provides crystalline particles with a small particle size distribution, enables a robust control of the particle size, and is easily scaled-up to a higher volume not taught or suggest by the cited reference. Applicants submit that the skilled artisan will not find any teaching or suggestion in Jakupovic that will teach him that the above-described technical problem can be solved by introducing the liquid medium comprising the compound(s) to be solidified into antisolvent(s) (or vice versa) by using a membrane positioned in a membrane module which membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres,

or spiral wounds. Furthermore, the skilled artisan would not have expected on the basis of Jakupovic that the process according to the present invention allows for the unexpected robust control of the particle size (page 5, lines 19-21) and yielding compositions having improved quality (see page 19, lines 23-27).

For these reasons, Jakupovic fails to disclose, teach or suggest the claimed invention of a process for preparing a solid composition whereby the process is carried out as a continuous process and the membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres, and spiral wounds, yielding a composition comprising solid particles comprising organic and/or inorganic compound(s). With respect to claim 16, applicants submit that the rejection is moot considering the cancellation of this claim. Accordingly, applicants respectfully request withdrawal of the rejection of claims 1-3, 5-8, 10, and 16.

3. Claim 4 is rejected under 35 U.S.C. § 103(a), as allegedly being obvious.

Claim 4 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jakupovic and further in view of Nocent et al., J. Pharm. Sci, 90, 1620-1627 (Nocent hereinafter) as set forth on pages 8-11 of the office action. According to the Examiner Nocent discloses a quasi-emulsion solvent diffusion method where the compound is dissolved in a solvent and the antisolvent phase is prepared separately and maintained at different temperatures. The Examiner asserts that Nocent discloses that incorporating in the crystallization process an emulsifier is attractive because it can lead to significant improvements in the physical properties of materials such as flowability, compressibility and compactibility. The disclosure in Nocent provides that a quasi-emulsion is formed in the process disclosed therein according to the Examiner. The Examiner asserts that the skilled artisan would have been motivated to combine the teachings in Jakupovic and Nocent, because Jakupovic teaches a process of solidification of chemical compounds by dissolving the compound in a solvent and passing it through a porous filter and adding it to an antisolvent for forming solid crystal particles and Nocent teaches a similar process. According to the Examiner, Nocent cures the failure in Jakupovic of forming an emulsion before solid particles are formed.

In response applicants submit that as discussed above Jakupovic fails to teach or suggest the claimed invention of a process for preparing a solid composition whereby the

process is carried out as a continuous process and the membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres, and spiral wounds, yielding a composition comprising solid particles comprising organic and/or inorganic compound(s). Although Nocent mentions the use of emulsions, Nocent does not teach or suggest a continuous anti-solvent solidification process whereby use is made of a membrane positioned in a membrane module which membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres, or spiral wounds, to admix a solution comprising material to be precipitated with an anti-solvent to precipitate the material. Thus the teachings in Nocent fail to cure the deficiency in the teachings of Jakupovic as described above.

Accordingly, the combination of Jakupovic and Nocent fails provide to the skilled artisan the process according to the presently claimed invention and does not teach or suggest that robust control of the particle size is possible and compositions having improved quality are obtained in such a process. Therefore, the cited references fail to teach or suggest the process of claim 4 either alone or in combination. Accordingly, applicants respectfully request withdrawal of the rejection of claim 4.

4. Claim 9 is rejected under 35 U.S.C. § 103(a), as allegedly being obvious.

Claim 9 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jukapovic as applied to claims 1-3, 5-8, 10, and 16 and further in view of Chen et al (US Patent 7,374,779, Chen hereinafter), as evidenced by Nakagawa et al. (Japan J. Pharmacol. 29, 509-514, 1979, Nakagawa hereinafter) as set forth on pages 11-13 of the office action. According to the Examiner Chen discloses a pharmaceutical formulation that provides increased absorption and bioavailability of active agents, particularly active agents that are administered orally. Further, according to the Examiner Chen discloses a list of active agents that includes preferred sex hormones such as progestins, such as 3-ketodesogestrel. The Examiner also asserts that the active agent can be dissolved in an appropriate solvent and subject to crystallization via precipitation by antisolvent. As illustrative example Chen discloses a formulation comprising progesterone. The Examiner asserts that the skilled artisan would be motivated to combine the teachings of Jakupovic and Chen because Chen teaches that the active agent can be dissolved in an appropriate solvent and subject to crystallization via precipitation by antisolvent to form pharmaceutical solid particles. According to the Examiner Chen cures the deficiency of Jakupovic in disclosing the

formation of progesterone or 3-ketodesogestrel crystal particles in the disclosed process, not taught or suggested by Jakupovic.

In response applicants submit that as discussed above Jakupovic fails to teach or suggest the claimed invention of a process for preparing a solid composition whereby the process is carried out as a continuous process and the membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres, and spiral wounds, yielding a composition comprising solid particles comprising organic and/or inorganic compound(s). Further, Chen discloses a pharmaceutical formulation comprising an active agent. The list of active agents includes among others: 3-Ketodesogestrel (column 10, line 24) Progesterone (column 10, line 29) Budesonide (column 14, line 47). Chen also discloses in column 54, lines 50 to 58, precipitation of the active agent by an anti-solvent.

However, applicants submit Chen does not disclose a continuous anti-solvent solidification process whereby use is made of a membrane positioned in a membrane module which membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres, or spiral wounds, to admix a solution comprising material to be precipitated with an anti-solvent to precipitate the material. Thus the teachings in Chen fail to cure the deficiency in the teachings of Jakupovic as described above.

Accordingly, the combination of Jakupovic and Chen (nor as evidenced by Nakagawa) fails provide to the skilled artisan the process according to the presently claimed invention and does not teach or suggest that robust control of the particle size is possible and compositions having improved quality are obtained in such a process. Therefore, the cited references fail to teach or suggest the process of claim 9 either alone or in combination. Accordingly, applicants respectfully request withdrawal of the rejection of claim 9.

5. Claims 11 and 12 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious.

Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jukapovic as applied to claims 1-3, 5-8, 10, and 16 and further in view of Maruyama et al (US Patent 5,512,092, Maruyama hereinafter) as set forth on pages 13-15 of the office action. According to the Examiner Maruyama discloses a method for preparing an aqueous emulsion for coating solid pharmaceutical preparations comprising the steps of dissolving a

cellulosic polymer in a mixed solvent of water and an organic solvent capable of being admixed with water in any rate to give a polymer solution, self-emulsifying the polymer solution by mixing with water and then concentrating the resulting emulsified stock solution. Further, according to the Examiner Maruyama discloses that the coating treatment is performed by spraying onto the solid particles. According to the Examiner the skilled artisan would have been motivated to coat the solid particles obtained in the process of Jakupovic because it will serve not only to protect a drug having low resistance to acids from the attack thereof in the stomach, but also protect the gastric mucous membrane from the attack of the drug which may stimulate and damage the wall of the stomach. Further, according to the Examiner the skilled artisan would be motivated to pass the coating solution through a membrane considering that the step would help to concentrate and adjust the concentration of the coating solution to a level as needed. The Examiner asserts that Maruyama cures the deficiency in Jakupovic with respect to a process of coating the solid particles which are formed.

In response applicants submit that as discussed above Jakupovic fails to teach or suggest the claimed invention of a process for preparing a solid composition whereby the process is carried out as a continuous process and the membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres, and spiral wounds, yielding a composition comprising solid particles comprising organic and/or inorganic compound(s). Further, Maruyama discloses in its abstract a method for preparing an aqueous emulsion which comprises the steps of dissolving a cellulosic polymer in a mixed solvent of water and an organic solvent capable of being admixed with water in any rate to give a polymer solution, self-emulsifying the polymer solution by mixing with water and then concentrating the resulting emulsified stock solution. The concentration is carried out by removing a part of the liquid components while passing it through a membrane for ultrafiltration till the polymer concentration of the resulting emulsion reaches a level of not less than 7% by weight.

The resulting aqueous emulsion is used to coat solid pharmaceutical preparations. The coating treatment is performed by spraying solid pharmaceutical preparations with the coating solution using a coating device and simultaneously drying the sprayed solution to form a coating film. Examples of coating devices usable herein include fluidized-bed coaters, pan-coaters, and air-vented rotary drum type coaters (column 4, lines 21 to 29).

Applicants submit however that Maruyama does not disclose a continuous anti-solvent solidification process whereby use is made of a membrane positioned in a membrane module which membrane has up to 3 μm pores and the shape of the membrane is selected from tubes, fibres, or spiral wounds, to admix a solution comprising material to be precipitated with an anti-solvent to precipitate the material. Thus the teachings in Maruyama fail to cure the deficiency in the teachings of Jakupovic as described above.

Accordingly, the combination of Jakupovic and Maruyama fails provide to the skilled artisan the process according to the presently claimed invention and does not teach or suggest that robust control of the particle size is possible and compositions having improved quality are obtained in such a process. Therefore, the cited references fail to teach or suggest the process of claim 11 and 12 either alone or in combination. Accordingly, applicants respectfully request withdrawal of the rejection of claim 11 and 12.

It is believed that claims 1-12, and 18-20 are now in condition for allowance, early notice of which would be appreciated. If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same.

Respectfully submitted,
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Dated: April 3, 2009

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